

DETECTION AND TREATMENT OF BREAST AND GYNECOLOGICAL CANCER

This application is filed under 35 U.S. C. §371 as a national stage application of the International application PCT/US94/11754, filed Oct. 14, 1994, which is a continuation-in-part of U.S. application Ser. No. 08/138,141, filed Oct. 15, 1993, now abandoned.

DESCRIPTION

1. Technical Field

The present invention relates to newly discovered antigens associated with breast and gynecological cancers and to immunoassay methods for detecting these antigens in biological samples, as well as immunotherapeutic methods for treating these cancers with antibodies that bind to these antigens. More specifically, the invention relates to the discovery of immunological cross-reactivity between antibodies to Human Immunodeficiency Virus (HIV-1) envelope protein gp120 and certain breast and gynecological carcinoma cell surface and chromatin antigens. This cross-reactivity results in the formation of new immunocomplexes which are useful in the immunodiagnostic methods of this invention.

2. Background

Breast carcinoma, together with carcinoma of the ovary, account for one-third of all cancers occurring in women, and together are responsible for approximately one-quarter of cancer-related deaths in females. Cancer of the female genital tract accounts for almost 80,000 cases of invasive cancer each year in the United States, with the majority of these being one of three neoplasms; carcinoma of the cervix, endometrial carcinoma, and celomic epithelial carcinoma of the ovary. Except for cervical cancer, which is definitely linked with Human Papilloma Virus infection, etiological agents involved in malignant transformation of breast, ovarian, or endometrial cells remain unclear. It has been established that susceptibility to breast and ovarian cancer is inherited in some families. Between 5% and 10% of breast cancer and ovarian cancer can be linked with inheritance of a gene conferring high risk, followed by genetic changes in epithelial cells. The gene which is believed to be responsible for inherited breast-ovarian cancer has been localized on the chromosome 17q12-21 and named locus BRCA 1; however, the sequences of the gene located in this locus are completely unknown. Approximately one in 200 women—600,000 women in the United States—have inherited susceptibility to breast cancer which is not only associated with BRCA1, but also with mutations in other genes like P53, Her2/erbB2, estrogen receptor and others. Genetic counseling for families with inherited susceptibility to breast and ovarian cancer and prophylactic mastectomy or oophorectomy represent a widely discussed subject.

Surgery, radiotherapy, and chemotherapy represent three basic methods which are used in management of breast cancer and gynecologic cancer. High mortality of breast cancer and gynecologic cancer patients indicates that the currently available diagnostic and therapeutic methods are unsatisfactory.

Immunotherapy and immunodiagnosis with monoclonal antibodies (MAb) represents another approach which has been extensively developing and improving during the past few years. In direct approaches, MAb IgG2a and IgG3 mediate antibody-dependent cellular cytotoxicity and/or exert complement-dependent cytotoxicity. Most frequently

used is radio-immunotherapy with radioactively labeled MAb. Immunotoxins, which are the conjugates of MAb with the subunit A of the ricin or diphtheria toxin, exhibit high tumoricidal potential, however have a restricted application due to high cytotoxicity.

Recently, a high number of monoclonal antibodies directed against breast, ovarian, and cervical cancer have been developed and efforts have been undertaken to use those MAbs as immunodiagnostic and immunotherapeutic agents. However, no significant progress has been reported in management of malignancies of the female reproductive tract using these techniques.

A number of HIV-1 peptides and proteins have been identified which elicit neutralizing antibodies in animals. EP-A-33504 describes chemically synthesized amino acid peptides having the sequence of amino acids from the HIV-1 virus which may be used to induce the production of HIV inhibiting antibodies for the treatment of AIDS and AIDS-related complex. However, the prior art has not disclosed a means of synthesizing and using monoclonal antibodies for purposes of detecting and treating breast and gynecological cancer.

It is an object of this invention to provide immunodiagnostic and immunotherapeutic methods which are believed to be an innovative approach to managing breast and gynecological cancers.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides methods for detecting the presence of HIV-1-crossreactive breast and gynecological cancer-associated antigens (as hereinafter defined) in biological samples and to methods for treating these cancers. In a preferred embodiment, these methods utilize a monoclonal antibody developed against a synthetic peptide corresponding to the variable domain of the Human Immunodeficiency Virus (HIV-1) envelope protein gp120 (amino acid region 308–322), herein referred to as MAb 5023. This MAb can be purchased from DuPont/NEN, 549 Albany Street, Boston Mass. 02118, and is listed in the catalog of this company entitled “DuPont/NEN Research Products 1992–1993” under Catalog Number, NEA-9305, the Product description of which is “HIV Monoclonal Antibody gp120-Neutralizing (sequence specific) (mouse) 0.5 mL”. In accordance with this invention, MAb 5023 has been found to be unique in its ability to penetrate the cell and localize within the cell nucleus and in its ability to recognize a family of antigens expressed by breast cancer and hynecological cancers.

Consequently, in accordance with this invention there is provided a method for diagnosis of breast cancer and hynecological cancer comprising exposing a biological sample from a host suspected of having said cancer to MAb 5023 and detecting the presence of HIV-crossreactive immunocomplexes. Fortuitously, this invention makes possible a simple and direct in vivo diagnosis of cervical cancer by administration of MAb 5023 to the cervix and then detecting the presence of immunocomplexes formed between said antibody and cell surface proteins p120 and p41 is another embodiment.

In one aspect of the invention, the method comprises detecting HIV-I-crossreactive breast carcinoma-associated antigens in a biological sample comprising (a) exposing a biological sample, suspected of containing the antigens, to an antibody which recognizes the following cell membrane proteins: p160, p80, p45, and p24 and the following chromatin protein: p24, and (b) detecting the presence of immunocomplexes formed between said antibody and said proteins.